Management of Multifocal and Multicentric Gliomas

Chirag G. Patil, MD, MS*, Paula Eboli, MD, Jethro Hu, MD

KEYWORDS

• Multifocal • Multicentric • Glioma • Glioblastoma
• Treatment

The diffuse nature of gliomas has long confounded attempts at achieving a definitive cure. Superradical hemispherectomies were performed in the early years of neurosurgery; yet even these desperate efforts could not prevent tumor from recurring on the contralateral side. With the advent of computed tomography and magnetic resonance imaging (MRI), it became increasingly apparent that gliomas could have a multifocal or multicentric appearance. Treating these tumors is the summit of an already daunting challenge, because the obstacles that must be surmounted to treat gliomas in general, namely, their heterogeneity, diffuse nature, and ability to insidiously invade normal brain, are more conspicuous in this subset of tumors.

EPIDEMIOLOGY

Malignant gliomas represent the most common primary brain tumor in adults. Median survival of patients with glioblastoma after optimal treatment continues to be less than 15 months.[1] Although most gliomas have been described as solitary lesions, multifocal/multicentric lesions have been described with an incidence ranging from 0.5% to 20%.[2–8] Most of the data available specifically regarding multifocal tumors are in the form of case reports or small series. Chamberlain and colleagues[9] described the radiographic patterns of relapse in 80 patients with glioblastoma multiforme (GBM). At diagnosis, 10% of patients had multifocal or multicentric disease, whereas at first recurrence this proportion increased to 14%. Salvati and colleagues[7] published a series on 25 patients with multicentric tumors and reported that these multicentric tumors represented 2% of all malignant tumors in their series. Silbergeld and colleagues[10] reported that 17% of 117 adult patients with supratentorial GBM examined post mortem by autopsy had multifocal disease.

Multicentric/focal gliomas can either be multiple at the time of diagnosis or develop later in the disease process. Kyritsis and colleagues[11] described 51 patients with multifocal/multicentric gliomas; 26 of the patients had simultaneous lesions at the time of diagnosis, whereas the other 25 developed multifocality later. In 14 of the 51 patients, no apparent dissemination route was identified, and the tumors were classified as multicentric gliomas. The rest of the patients showed different patterns of spread from the primary site, and the tumors were classified as multifocal. The investigators described the meningeal-subarachnoid space as the most frequent dissemination route, followed by the subependymal route, intraventricular route, and direct brain penetration.[11]

DEFINITION: MULTIFOCAL VERSUS MULTICENTRIC TUMORS

Multicentric gliomas were first described by Bradley[12] in 1880. Based on the points brought up by Russell and Rubinstein, Batzdorf and Malamud[2] described the criteria to differentiate multifocal from multicentric tumors in 1963. The investigators described multifocal tumors as those that can be explained as the result of growth or dissemination via established routes: (1) commissural or other

Department of Neurological Surgery, Cedars-Sinai Medical Center, Los Angeles, CA, USA
* Corresponding author. Center for Neurosurgical Outcomes Research, Maxine Dunitz Neurosurgical Institute, Department of Neurosurgery, Cedars-Sinai Medical Center, 8631 West Third Street, Suite 800E, Los Angeles, CA 90048.
E-mail address: chiragpatil@gmail.com

Neurosurg Clin N Am 23 (2012) 343–350
doi:10.1016/j.nec.2012.01.012

pathways, such as the corpus callosum; (2) cerebrospinal fluid channels, either through subarachnoid spaces or the ventricular system; and (3) local metastasis through satellite formation in the immediate vicinity of the main tumor. Multicentric tumors were defined as those that represent widely separated lesions, for example, those in different hemispheres and whose origin cannot be explained following the pathways mentioned earlier. Multicentric tumors also include those tumors separated in time.[2] Although these definitions can be used to separate patients with multifocal gliomas from those that harbor multicentric tumors, the clinical or prognostic significance between these 2 clinical entities remains unclear.

PATHOGENESIS

The pathogenesis of multicentric tumors is unknown. In 1960, Willis[13] introduced the theory of initiation and promotion that allows unlinked proliferation of neoplastic cells at different topographic locations[4] and suggested that multicentric lesions could result from a 2-step process. In the first stage called initiation, a large area or perhaps the entire brain undergoes neoplastic transformation and becomes more susceptible to neoplastic growth. In the second stage called promotion, the neoplastic proliferation occurs in multiple sites through different sources of stimulation, such as hormonal, biochemical, or even viral.[14,15] The increased prevalence of multicentric tumors in patients with germline p53 mutations and neurofibromatosis type I (with germline mutation of the *NF1* tumor suppressor gene) is likely explained by the mechanism by which the germline mutation serves as the initiating hit.[16,17] The idea of initiation and promotion also makes sense in the context of the cancer stem cell hypothesis, as elaborated later.

Despite this theory, most cases of multicentric tumors and all cases of multifocal tumors are more likely to develop because of the unique propensity of glioma cells to invade normal brain and migrate long distances. (Claes and colleagues[15] aptly compared glioma cells to guerilla warriors capable of invading individually or in small groups and abusing preexisting supply lines.) In 1940, the neuropathologist Hans-Joachim Scherer[18] described secondary structures of glioma growth along existing cytoarchitectural elements, such as neurons, white matter tracts, and blood vessels. In 1997, Geer and Grossman[19] suggested that interstitial fluid flow along white matter tracts could be a potentially important mechanism for the dissemination of glioma cells, explaining that glioma cells are inherently capable of migration along white matter tracts to distant areas of the brain. Hefti and colleagues[4] found most multicentric glioma lesions to be located along known migrational pathways of glioma cells and, therefore, suggested that active migratory processes are involved in the development of these lesions. The investigators also described a time-related dependency for multicentricity and concluded that with the advent of radical tumor resection, adjuvant therapies, better local control, and longer life expectancy, the incidence of multicentric/multifocal gliomas is likely to increase.

PATHOLOGY

Pathologically, most multicentric/multifocal gliomas can be classified as GBM.[2,7] However, anaplastic astrocytoma, anaplastic oligoastrocytoma, gliosarcoma, oligodendroglioma, and ependymoma with multicentric and multifocal features have been described.[2,7,20] These tumors do not exhibit any specific histologic features that could differentiate them from similar unifocal gliomas.[2] In most cases, the histology of separate lesions is similar, with variations comparable to those visualized in different areas of the same tumor.[2] However, less commonly, multicentricity can also occur as a combination of different histologic tumors, for example, anaplastic astrocytoma and glioblastoma, low-grade astrocytoma and anaplastic astrocytoma, and low-grade astrocytoma and glioblastoma.[5,7,21] Most multicentric gliomas occur supratentorially, but combined lesions in both supratentorial and posterior fossa have also been described.[2,7,8,22,23]

DIAGNOSIS

MRI with contrast is the modality of choice for evaluating brain tumors. Glioblastomas, brain metastases, and central nervous system (CNS) lymphomas share similar enhancement patterns on MRI, and no definitive characteristics can differentiate multifocal/multicentric GBM from metastatic disease or CNS lymphoma.[3,22,24] Very recently, Wang and colleagues[25] reported the use of a combination of MRI diffusion tensor imaging (DTI) and dynamic susceptibility contrast-enhanced (DSC) MRI to differentiate glioblastomas from metastases and lymphoma. Using DTI and DSC parameters, the investigators were able to differentiate GBM from metastases and lymphoma with a sensitivity of 89% and specificity of 93%.

Although important strides are being made to radiographically differentiate between these pathologic conditions, tissue diagnosis with surgical biopsy remains the standard of care for all gliomas including multifocal/multicentric tumors.

TREATMENT

Surgical Management

There are no clearly defined guidelines in the literature on the surgical management of multifocal or multicentric gliomas. Some investigators favor a conservative surgical approach with the use of stereotactic biopsy for accurate diagnosis while avoiding risk of neurologic deficit or hemorrhage.[22,26] Other investigators have suggested that aggressive resection of the contrast-enhancing portions of multifocal/multicentric tumors yields better overall survival compared with patients with solitary malignant gliomas. These investigators have recommended craniotomy or even multiple craniotomies with maximal safe resection.[3,7]

Hassaneen and colleagues[3] recently described the use of multiple craniotomies in the management of multifocal and multicentric glioblastomas in 20 patients and used a matched cohort of patients with solitary GBM for comparison. The investigators, however, were not able to compare their results with those of a group of patients with multicentric/multifocal glioblastomas who were treated only with biopsy. An overall survival of 9.7 months was reported in the multifocal/multicentric group after aggressive surgical resection with multiple craniotomies. This result was similar to that of the matched control group with single tumors who had a median survival of 10.5 months ($P = .34$). The investigators concluded that multiple craniotomies resulted in a survival period comparable with that of patients undergoing surgery for a single lesion, with no increase in complication rate or postoperative morbidity.[3] Therefore, these investigators recommended maximal safe resection of the enhancing tumors to maximize survival in select patients with multifocal/multicentric tumors.

Salvati and colleagues[7] described the largest series of 25 patients with multicentric high-grade gliomas according to the criteria defined by Batzdorf and Malamud.[2] In their series, similar to Hassaneen and colleagues,[3] the average survival of patients who underwent surgical resection was 9.5 months. Patients with tumors in inaccessible or eloquent locations underwent biopsy and had an average survival of 2.8 months. Based on their data and experience, the investigators concluded that patients with accessible tumors should undergo surgical resection of all tumors and the rest should undergo stereotactic biopsy to obtain histologic diagnosis.[7]

Radiation Therapy

The standard treatment of malignant glioma, specifically GBM, involves conformal radiotherapy (RT) of 60 Gy encompassing the tumor volume and margin. However, historically, whole brain radiotherapy (WBRT) has been used for the treatment of multifocal/multicentric tumors with or without a boost to the tumor. The inclusion of whole brain fields has been recently questioned, given that most failures occur within the original tumor volume and that limited doses can be delivered to the entire brain.[27]

Showalter and colleagues[27] reported outcomes of 50 patients with multifocal or multicentric GBMs who were treated with WBRT (n = 16) or conformal RT (n = 34). The median survival was 8.1 months. The investigators found no difference in the time to progression or overall survival in patients treated with WBRT versus those treated with conformal RT. All patients had local recurrence, and no recurrences were seen distant from the original foci in the absence of significant local progression. Therefore, the investigators concluded that conformal RT is as efficacious as WBRT and that radiation of whole brain fields may not be necessary.[27] A limited field radiation may better optimize cognitive outcomes and functional status, given the evidence of decline in neurocognitive outcomes in patients undergoing WBRT for brain metastases.[28]

The efficacy of stereotactic radiosurgery (SRS) in the treatment of malignant gliomas is not clearly established. Several retrospective reviews suggest a survival benefit when SRS is used after conventional RT for focal residual or recurrent disease. For example, Pouratian and colleagues[29] reported a median survival of 16.2 months in 48 patients with GBM who underwent Gamma Knife radiosurgery and concluded that this suggests an improved survival compared with the median survival of 14.6 months reported by the pivotal randomized controlled trial by Stupp and colleagues.[1] However, the only randomized controlled trial assessing the efficacy of SRS before RT failed to show any benefit.[30] Many investigators, however, continue to believe that SRS has a role in the management of patients after RT for small, residual, inaccessible, or recurrent foci.[29,31]

Chemotherapy

There is currently no clinically proven chemotherapy that specifically targets multifocal or multicentric glioblastoma. In general, the standard treatment of a newly diagnosed glioblastoma consists of fractionated involved-field radiation therapy combined with the oral alkylating agent temozolomide, followed by cycles of adjuvant temozolomide. An international phase III trial demonstrated a median survival of 14.6 months with this regimen.[1] Many patients with glioblastoma

are also treated at some point with the antiangiogenic agent bevacizumab. Bevacizumab, an intravenously administered monoclonal antibody, inhibits the vascular endothelial growth factor (VEGF) and was approved by the Food and Drug Administration, in 2009, for the treatment of recurrent glioblastoma. Although the survival benefit is modest, treatment with bevacizumab is well tolerated and often improves quality of life.

Great effort has gone into identifying subpopulations of patients who may respond better (or worse) to a particular treatment. It is now well established that patients with tumors that possess a methylated *O*6-methylguanine-DNA methyltransferase (MGMT) promoter are more likely to respond well to chemotherapy with temozolomide than those with tumors that possess an unmethylated MGMT promoter.[32,33] Yet temozolomide is the current first-line chemotherapeutic agent for patients with tumors that possess an unmethylated MGMT promoter. Our therapeutic armamentarium is not currently robust or sophisticated enough to further tailor treatments, and the same holds true for the subset of patients with multifocal/multicentric glioblastoma; they may not do as well as the others, but clearly no better treatment option exists. In addition, with the ability to hit a near-limitless number of targets, chemotherapy holds great promise. Furthermore, we can use our knowledge of pathophysiology to design rational treatment strategies for patients with multifocal/multicentric glioblastoma. Promising areas of research include targeting invasion, targeting glioma stem-like cells, and using immunotherapy.

Targeting invasion

Tumor invasion confounds traditional modes of treatment in multiple ways. Locally directed therapies, such as surgical resection and intracavitary therapies, may not reach the leading invasive edge of the tumor. This inaccessibility is obviously the case with multifocal/multicentric tumors. In addition, the blood-brain barrier is much more likely to be intact along the leading edge of the tumor, which poses a significant challenge for systemically delivered therapies. Only 2% of low–molecular weight drugs (and no high–molecular weight drugs) are able to penetrate an intact blood-brain barrier.[34] Lastly, several lines of evidence suggest that invasiveness and proliferation are inversely correlated. Tumor growth factor β, for example, stimulates invasion but suppresses proliferation.[35] Furthermore, glioma cells selected for their migratory capacity in vitro demonstrate a slower growth rate than their unselected counterparts, and analysis of glioma biopsies has shown decreased proliferation rates in the white matter and infiltrated cortex compared with solid tumor.[36,37] Most traditional chemotherapy drugs are selectively toxic to cells that divide rapidly. Therefore, in addition to being exposed to less chemotherapy, tumor cells along the invasive edge are also less susceptible to the effects of chemotherapy.

There has also been concern that treatment with antiangiogenic agents may promote tumor invasiveness. In 2001, Kunkel and colleagues[38] showed that when mice implanted with human G55 glioma cells were treated with DC101 (a monoclonal antibody against VEGF receptor 2), the number of satellite tumors increased significantly, even though the overall tumor volumes were reduced. On histopathologic examination, tumor cells were seen migrating long distances along host vessels and in the subarachnoid space. Several retrospective reviews of imaging patterns at recurrence after antiangiogenic therapy seemed to further justify this concern. In a review of 26 patients treated with bevacizumab, Norden and colleagues[39] reported that 4 patients (15%) presented with distant disease at relapse. Similarly, Iwamoto and colleagues[40] found that 6 of 37 patients (16%) treated with bevacizumab had multifocal disease at relapse. Only 46% of the patients in this bevacizumab-treated group developed enhancing local disease at relapse, much lower than the 90% to 95% rate of local recurrence reported in studies performed in the preantiangiogenic era. These studies suggest that multifocal/multicentric disease may become more commonplace now that antiangiogenic therapy is well established. However, subsequent studies have not found an increased risk of remote or multifocal relapse after treatment with bevacizumab.[9,41] Regardless of whether antiangiogenic therapy itself increases the risk of multifocal/multicentric disease, it seems likely that as median survival continues to improve and more patients survive beyond first, second, and third relapses, the incidence of multifocal/multicentric disease will increase.

Invasion requires the coordination of several distinct cellular processes, each of which can potentially be targeted. First, glioma cells must dissociate from the tumor mass and form contacts with the extracellular matrix (ECM). CD44, tenascin-C, neural cell adhesion molecule, cadherins, and integrins play critical roles in this process. In a rat gliosarcoma model, intratumoral injection of an anti-CD44 monoclonal antibody resulted in decreased brain invasion.[42] Tenascin-C is an ECM glycoprotein that is ubiquitously expressed by glioma cells. A radiolabeled monoclonal antibody against tenascin-C has been developed,

but the intracavitary injection used to deliver this treatment may fail to reach the leading invasive edge it was designed to target. The cyclic pentapeptide cilengitide is an inhibitor of the integrins $\alpha_v\beta_3$ and $\alpha_v\beta_5$. These integrins are expressed on both endothelial and glioma cells, suggesting that cilengitide may target both angiogenesis and invasion. Having demonstrated activity and safety in several phase I and II trials, cilengitide is currently being evaluated in phase III trials for the treatment of patients with glioblastoma.

After detachment from the tumor mass, the ECM must be degraded and remodeled to allow for cell movement. This process involves matrix metalloproteinases (MMPs), urokinase plasminogen activator and its receptor, cathepsin, and the family of multidomain membrane-associated proteins known as a disintegrin and metalloproteinase. A randomized placebo-controlled phase II trial of the MMP inhibitor marimastat showed negative results, perhaps because of compensatory activity by other enzymes.[43]

Finally, the cellular machinery responsible for cell migration must be activated. For movement to occur, lamellipodia and filopodia interact with the ECM at adhesion complexes. These complexes consist of an integrin core in association with numerous other proteins, including focal adhesion kinase (FAK), which has been shown to be overexpressed in glioma, particularly at the infiltrating edge. In vitro studies demonstrate that inhibiting FAK decreases invasiveness.[44]

The initiation and coordination of cellular processes that lead to invasion result from activation of specific signal transduction pathways. In particular, the receptor tyrosine kinases, epidermal growth factor receptor (EGFR) and c-Met, as well as the nonreceptor tyrosine kinase Src drive glioma invasiveness, although all these pathways have pleiotropic effects beyond triggering invasion. The small molecule EGFR inhibitors erlotinib and gefitinib have been evaluated in multiple clinical trials for glioblastoma, with only modest results. An earlier study suggested that EGFR inhibitors may be more effective for tumors that possess the EGFRvIII mutation and wild-type PTEN, but subsequent studies have not validated this finding.[45] In a small retrospective review, the multikinase inhibitor dasatinib (which inhibits Src, BCR-ABL, c-KIT, ephrin type-A receptor 2, and platelet-derived growth factor β) demonstrated little activity after bevacizumab failure in patients with heavily pretreated GBM.[46] Results of multicenter clinical trials on dasatinib are currently pending. Rilotumumab, a monoclonal antibody against hepatocyte growth factor/scatter factor, the ligand for c-Met, was recently evaluated in a phase II clinical trial for patients with recurrent glioblastoma. Again, little activity was seen.[47] The overall lack of efficacy seen in clinical trials to date may be because of coactivation of multiple signaling pathways. Combination therapy may, therefore, be required.

Targeting glioma stem-like cells

In 2003, Singh and colleagues[48] demonstrated that cancer cells with stem-like properties are present within brain tumors. Unlike the more differentiated cells that comprise the bulk of a tumor, cancer stem cells are capable of continual proliferation and self-renewal. Because these cells are relatively quiescent, they are resistant to radiation therapy and traditional cytotoxic chemotherapy. It has long been thought that these glioma stem-like cells may preferentially reside in specific niches such as the subventricular zone (SVZ) in which nonneoplastic neural stem cells are known to exist. Glantz and colleagues[49] theorize that the inability of locally directed therapies to permanently eradicate tumor may be because of the continued presence of glioma stem-like cells in the SVZ. These cells may possess the ability to migrate out of the SVZ into the surrounding brain tissue far away from the primary tumor using the same scaffolding used in neural development. Lim and colleagues[50] showed that glioblastomas contacting the SVZ and infiltrating cortex are much more likely to have multifocal disease (56%) at diagnosis than tumors found in other locations. Multifocal/multicentric tumors may, therefore, be more enriched with glioma stem-like cells than their solitary counterparts, thus adding to the treatment challenge.

Even as the cancer stem cell hypothesis is being debated and refined, targeting glioma stem-like cells has become an area of active research. Normal stem cells are regulated by signaling pathways that play an important role in development, such as the SHH, Wnt, and Notch signaling pathways. Dysregulation of these pathways can lead to the development of cancer stem cells, and inhibitors of these pathways are currently being evaluated for clinical use. Nitric oxide signaling has recently been shown to play an important role in glioma stem cell proliferation.[51] A multicenter phase II dendritic cell vaccine trial in which the autologous dendritic cells used in the vaccine are primed against antigens that are highly expressed by cancer stem cells is currently underway. Glantz and colleagues[49] suggest that because glioma stem-like cells may reside in the SVZ, cerebrospinal fluid (CSF)-directed therapies may have better efficacy than systemically delivered therapies. Chemotherapeutic agents instilled directly into the CSF only penetrate a few

millimeters into the brain parenchyma, so the efficacy of this strategy is unclear. To date, no clinically proven method of eradicating glioma stem-like cells exists.

Immunotherapy

One of the most promising areas of oncology research is immunotherapy, and the immunotherapeutic approach may prove to be a particularly effective strategy against multifocal/multicentric glioblastoma. After all, few, if any, pharmaceutical compounds are able to seek out and destroy foreign pathogens as robustly and specifically as the immune system. Several clinical trials using immune-priming adjuvant therapies (such as polylysine and carboxymethylcellulose, a toll-like receptor 3 ligand) or dendritic cell vaccines have been performed or are underway. To date, no trial results that specifically address efficacy for multicentric/multifocal gliomas have been reported. However, using a rat multifocal glioblastoma model (in which rats were injected with glioma cells in each hemisphere), King and colleagues[52] demonstrated that treatment with adenoviral vectors expressing thymidine kinase and human Flt3L resulted in long-term survival in 50% of the animals. By recruiting macrophages and CD4 cells, the presence of Flt3L helps initiate an immune response that is able to eradicate distant targets. A clinical trial of this therapy is about to commence.

PROGNOSIS

Multifocal and multicentric gliomas have traditionally been thought to have a worse prognosis than solitary tumors. The median survival for these patients has ranged from 2 to 10 months.[3,7,14,27] Salvati and colleagues[7] reported a median survival of 2.8 months for patients who underwent biopsy of their multicentric tumors. These patients had tumors located in inaccessible or eloquent regions. Patients with surgically accessible tumors who underwent surgical resection had a median survival of 9.5 months.[7] Similarly, Hassaneen and colleagues[3] reported a median survival of 9.7 months after aggressive surgical management and concluded that if the enhancing portions of the multifocal/multicentric tumors can be safely resected, outcomes in these patients may be similar to those in patients with solitary disease. Finally, Showalter and colleagues[27] studied 50 patients who underwent RT and multiple therapies for their multifocal malignant gliomas and described a median survival of 8.1 months.

SUMMARY

Multifocal and multicentric tumors magnify many of the challenges one faces when treating patients with malignant gliomas. Issues such as biopsy versus maximal safe resection and optimal choice of anticancer treatments beyond the standard of care are currently under debate and investigation. The subset of patients with multifocal or multicentric gliomas may indeed be more susceptible or resistant to a given therapy compared with those with localized disease. As the knowledge of the disease process increases, the ability to better tailor treatments will also improve.

REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96.
2. Batzdorf U, Malamud N. The problem of multicentric gliomas. J Neurosurg 1963;20:122–36.
3. Hassaneen W, Levine NB, Suki D, et al. Multiple craniotomies in the management of multifocal and multicentric glioblastoma. Clinical article. J Neurosurg 2011;114:576–84.
4. Hefti M, von Campe G, Schneider C, et al. Multicentric tumor manifestations of high grade gliomas: independent proliferation or hallmark of extensive disease? Cen Eur Neurosurg 2010;71:20–5.
5. Jaskolski D, Zawirski M, Wisniewska G, et al. A case of multicentric glioma of cerebellum and brain. Zentralbl Neurochir 1988;49:124–7.
6. Kato T, Aida T, Abe H, et al. Clinicopathological study of multiple gliomas—report of three cases. Neurol Med Chir (Tokyo) 1990;30:604–9.
7. Salvati M, Caroli E, Orlando ER, et al. Multicentric glioma: our experience in 25 patients and critical review of the literature. Neurosurg Rev 2003;26:275–9.
8. Solomon A, Perret GE, McCormick WF. Multicentric gliomas of the cerebral and cerebellar hemispheres. Case report. J Neurosurg 1969;31:87–93.
9. Chamberlain MC. Radiographic patterns of relapse in glioblastoma. J Neurooncol 2011;101:319–23.
10. Silbergeld DL, Rostomily RC, Alvord EC Jr. The cause of death in patients with glioblastoma is multifactorial: clinical factors and autopsy findings in 117 cases of supratentorial glioblastoma in adults. J Neurooncol 1991;10:179–85.
11. Kyritsis AP, Levin VA, Yung WK, et al. Imaging patterns of multifocal gliomas. Eur J Radiol 1993;16:163–70.
12. Bradley WL. Case of gliosarcomatous tumors of the brain. Proc Conn Med Soc 1880;2:39–41.
13. Willis RA. Pathology of tumors. London: Butterworths; 1960. p. 811.
14. Ampil F, Burton GV, Gonzalez-Toledo E, et al. Do we need whole brain irradiation in multifocal or multicentric high-grade cerebral gliomas? Review of

cases and the literature. J Neurooncol 2007;85: 353–5.
15. Claes A, Idema AJ, Wesseling P. Diffuse glioma growth: a guerilla war. Acta Neuropathol 2007;114: 443–58.
16. Kyritsis AP, Bondy ML, Xiao M, et al. Germline p53 gene mutations in subsets of glioma patients. J Natl Cancer Inst 1994;86:344–9.
17. Kyritsis AP, Yung WK, Leeds NE, et al. Multifocal cerebral gliomas associated with secondary malignancies. Lancet 1992;339:1229–30.
18. Scherer H. Structural development in gliomas. Am J Cancer 1938;34:333–51.
19. Geer CP, Grossman SA. Interstitial fluid flow along white matter tracts: a potentially important mechanism for the dissemination of primary brain tumors. J Neurooncol 1997;32:193–201.
20. Bassoe P. Multiple ependymal glioma—one tumor of the fourth ventricle, the other of the frontal lobes. Arch Intern Med 1908;2:194–200.
21. Salunke P, Badhe P, Sharma A. Cerebellar glioblastoma multiforme with non-contiguous grade 2 astrocytoma of the temporal lobe in the same individual. Neurol India 2010;58:651–3.
22. Chadduck WM, Roycroft D, Brown MW. Multicentric glioma as a cause of multiple cerebral lesions. Neurosurgery 1983;13:170–5.
23. Mishra HB, Haran RP, Singh JP, et al. Multicentric gliomas: two case reports and a review of the literature. Br J Neurosurg 1990;4:535–9.
24. Wang S, Kim S, Chawla S, et al. Differentiation between glioblastomas and solitary brain metastases using diffusion tensor imaging. Neuroimage 2009;44:653–60.
25. Wang S, Kim S, Chawla S, et al. Differentiation between glioblastomas, solitary brain metastases, and primary cerebral lymphomas using diffusion tensor and dynamic susceptibility contrast-enhanced MR imaging. AJNR Am J Neuroradiol 2011;32:507–14.
26. Marshall LF, Jennett B, Langfitt TW. Needle biopsy for the diagnosis of malignant glioma. JAMA 1974; 228:1417–8.
27. Showalter TN, Andrel J, Andrews DW, et al. Multifocal glioblastoma multiforme: prognostic factors and patterns of progression. Int J Radiat Oncol Biol Phys 2007;69:820–4.
28. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 2009;10: 1037–44.
29. Pouratian N, Crowley RW, Sherman JH, et al. Gamma Knife radiosurgery after radiation therapy as an adjunctive treatment for glioblastoma. J Neurooncol 2009;94:409–18.
30. Souhami L, Seiferheld W, Brachman D, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. Int J Radiat Oncol Biol Phys 2004;60:853–60.
31. Elliott RE, Parker EC, Rush SC, et al. Efficacy of gamma knife radiosurgery for small-volume recurrent malignant gliomas after initial radical resection. World Neurosurg 2011;76:128–40 [discussion: 161–2].
32. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352:997–1003.
33. Hegi ME, Liu L, Herman JG, et al. Correlation of O6-methylguanine methyltransferase (MGMT) promoter methylation with clinical outcomes in glioblastoma and clinical strategies to modulate MGMT activity. J Clin Oncol 2008;26:4189–99.
34. Pardridge WM. Blood-brain barrier drug targeting: the future of brain drug development. Mol Interv 2003;3:90–105, 151.
35. Merzak A, McCrea S, Koocheckpour S, et al. Control of human glioma cell growth, migration and invasion in vitro by transforming growth factor beta 1. Br J Cancer 1994;70:199–203.
36. McDonough W, Tran N, Giese A, et al. Altered gene expression in human astrocytoma cells selected for migration: I. Thromboxane synthase. J Neuropathol Exp Neurol 1998;57:449–55.
37. Schiffer D, Cavalla P, Dutto A, et al. Cell proliferation and invasion in malignant gliomas. Anticancer Res 1997;17:61–9.
38. Kunkel P, Ulbricht U, Bohlen P, et al. Inhibition of glioma angiogenesis and growth in vivo by systemic treatment with a monoclonal antibody against vascular endothelial growth factor receptor-2. Cancer Res 2001;61:6624–8.
39. Norden AD, Young GS, Setayesh K, et al. Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. Neurology 2008;70:779–87.
40. Iwamoto FM, Abrey LE, Beal K, et al. Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma. Neurology 2009;73:1200–6.
41. Wick A, Dörner N, Schäfer N, et al. Bevacizumab does not increase the risk of remote relapse in malignant glioma. Ann Neurol 2011;69:586–92.
42. Gunia S, Hussein S, Radu DL, et al. CD44s-targeted treatment with monoclonal antibody blocks intracerebral invasion and growth of 9L gliosarcoma. Clin Exp Metastasis 1999;17:221–30.
43. Levin VA, Phuphanich S, Yung WK, et al. Randomized, double-blind, placebo-controlled trial of marimastat in glioblastoma multiforme patients following surgery and irradiation. J Neurooncol 2006;78:295–302.
44. Liu TJ, LaFortune T, Honda T, et al. Inhibition of both focal adhesion kinase and insulin-like growth factor-I receptor kinase suppresses glioma proliferation in vitro and in vivo. Mol Cancer Ther 2007;6:357–1367.

45. Mellinghoff IK, Wang MY, Vivanco I, et al. Molecular determinants of the response of glioblastomas to EGFR kinase inhibitors. N Engl J Med 2005;353: 2012–24.
46. Lu-Emerson C, Norden AD, Drappatz J, et al. Retrospective study of dasatinib for recurrent glioblastoma after bevacizumab failure. J Neurooncol 2011;104:287–91.
47. Wen PY, Schiff D, Cloughesy TF, et al. A phase II study evaluating the efficacy and safety of AMG 102 (rilotumumab) in patients with recurrent glioblastoma. Neuro Oncol 2011;13:437–46.
48. Singh SK, Clarke ID, Terasaki M, et al. Identification of a cancer stem cell in human brain tumors. Cancer Res 2003;63:5821–8.
49. Glantz M, Kesari S, Recht L, et al. Understanding the origins of gliomas and developing novel therapies: cerebrospinal fluid and subventricular zone interplay. Semin Oncol 2009;36:S17–24.
50. Lim DA, Cha S, Mayo MC, et al. Relationship of glioblastoma multiforme to neural stem cell regions predicts invasive and multifocal tumor phenotype. Neuro Oncol 2007;9:424–9.
51. Eyler CE, Wu Q, Yan K, et al. Glioma stem cell proliferation and tumor growth are promoted by nitric oxide synthase-2. Cell 2011;146:53–66.
52. King GD, Muhammad AK, Curtin JF, et al. Flt3L and TK gene therapy eradicate multifocal glioma in a syngeneic glioblastoma model. Neuro Oncol 2008;10:19–31.